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A hand is shown from the bottom, holding a glowing blue and white globe of the Earth. The background is a dark blue digital interface with various data visualizations, including bar charts, line graphs, and text boxes. Labels like 'BUSINESS', 'NETWORK SEARCH', and 'WORLD' are visible. The overall aesthetic is futuristic and technological.

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G-quadruplex Scaffold Potential Target for Tumors by Stabilizing the Guanine Bases Repeats: Comprehensive Review

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ABSTRACT: G-4 (Guanine containing-quadruplex) is highly specialized non-canonical motif related to Genetic material (DNA). G-4, clearly recognize that its involvement into replication of many cancerous cells, apart from whole central dogma process in cancer-related genes. Hence, targeting G-4 has become a new promising area for anti-cancer drug development. Targeting G4 through low molecular weight molecules targeting the G-4 have been designed, synthesized, verified to immense use against tumor cells, it involves that molecule directly stack to the G-4 non canonical motif. The significance role of G-quadruplex motif acting as anti-cancer drugs especially in metastatic cancer. Indeed helicase is an enzymatic protein, which is more specific towards G-4 scaffold, emerging target like helicase in case of G-4 motif is big deal to design specific small scaffold that helps in hacking cancer problem since Elizabeth discovery of G-4.

KEYWORDS: G-quadruplex, Motif, Minor Groove, Small Molecules, DNA double strand.

I. INTRODUCTION

G-quadruplex scaffold

DNA is the genetic material having the specialized double-helical structure it found in eukaryotic as well as in somatic cells [1]. The fundamental function of telomerase to protect the genomic end by the maintaining length [2]. During replication of the cells leads to erosion of telomers approximately 50-200 base pair loss during every single round of somatic cell division [3]. The secondary scaffold of G-quadruplex classified into unimolecular, bimolecular, trimolecular and tetra-molecular it formed by DNA and RNA based upon the sequence. However it shows the various morphological strand by orienting themselves, it shows variation in their number G strand number of stack central part and length also shows type variation. In the corresponding to G quadruplex, it includes four parallel or antiparallel direction and its related to the conformational changes and glycosidic torsion angle, in case of parallel G quadruplex all legs in contrary route it has both syn and anti- guanine. G-quadruplex has some promise like, when three legs in the same direction called syn-syn-syn-anti confirmation vice-versa, also known as hybrid mixed G- tetrad core.

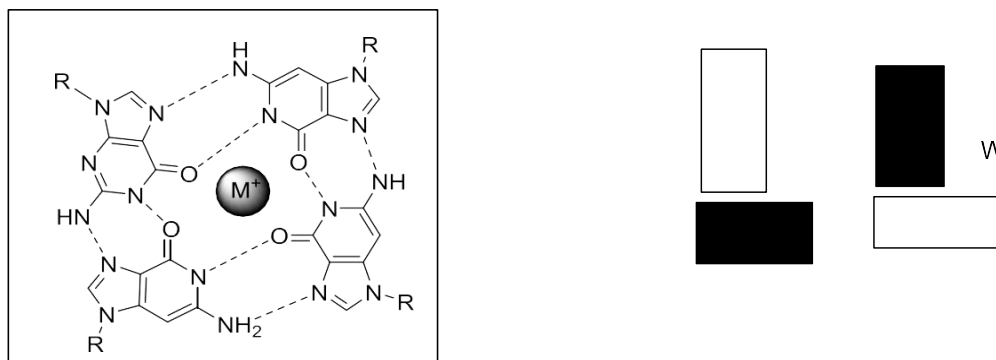


Figure:1 Guanine arrangement with metal cation.

The secondary scaffold categorizes into unimolecular, bimolecular, trimolecular and tetra-molecular it formed by DNA and RNA rely upon the sequence. However it shows the various morphological strand by orienting themselves, its shows variation in their number G strand number of stack central part and length also shows type variation. In the corresponding to G quadruplex, it includes four parallel or antiparallel direction and its related to the conformational changes and glycosidic torsion angle, in case of parallel G quadruplex all legs in contrary route it has both syn and anti guanine. G-quadruplex has some promise like, when three legs in the same direction called syn-syn-syn-anti confirmation vice-versa, also known as hybrid mixed G- tetrad core [4].

Unimolecular G-quadruplex

G quadruplex can implement the various kind of the significant turns like , the diagonal type loop, lateral side loop and last is the external loop. It can crease into a parallel tetrad with three G-quadruplex loops [5]. For Instance, human telomeric sequences form crystal structure through the reappearance of the d[AG3(T2AG3)3]. It is also called a hybrid G-quadruplex, by orient themselves in the same and one is a conflicting path, that further agrees to anti-anti-anti-syn confirmation. It also surrounds one narrow and wide external loop. The adaptability of the confirmation depends on their situation and cationic environment. The quadruplex has Watson- crick duplex in a long loop that may a crucial part of the novel target. The identification of that the c-Myc2345, oncogene promoter sequence contains 22 nucleotides and c-Myc 1245, 5'-TGAG3TG4AG3TG4A2-3' these two sequences are formed by intra-molecular G-4 scaffold similar to the human telomeric genome. The extend beyond of telomeric gene segment made of mono duplicate of the TTAGGG unit of something like 100-200 base pair in biological system.

Tetrad G-quadruplex

The G-quadruplex family it fashioned from single frequent guanine containing sequences. In G- quadruplex type four, it showed their crystal structure that each and every one of four legs are corresponding and anti-affirmation has no loop [18]. However, it contains four groove and its RNA parts. The explication of the G-quadruplex type four by NMR, UV spectroscopy having d(GGGT), G- quadruplex [19]. The further G tetrads at the boundary in between two were accomplished by the free guanine at 5'-end of G4 monomer [2+2 type] [20]. The subsistence and determination of the G- quadruplex construction have been established by the anthropological genome. in the region of 370000 DNA bp are found in the anthropological genome [21]. The G quadruplex DNA created from the telomeric region and inhibits the telomeres activity. Polymorphism of this configuration mainly results from their direction of the strand length DNA and position. There is some challenges at the morphological intensity, G quadruplex fashioned structure through the assortment of the long double helical strand. an additional is it formed at from three guanine-rich stand. The consequence of the natural role of G quadruplex occupies and they are great probable, for stabilization G-quadruplex small molecules have crucial drug- like properties. The current innovation walk around the conspirator molecules may correspond to a new class of drugs that stack the guanine-rich workstation. Apart from the natural meaning there so many challenges like to start on with to fussiness intended for G-4 over double helical DNA but giving to the subclass of the G-4 scaffold [22].

In the vivo G4 scaffold adopt the human gene sequences below bio-physi significant circumstance is still indecisive therefore, some of reports have not compulsory crossed link structure to be the major alteration inside biological circumstance [6].

The telomeric length is completed by enzyme telomerase which is overexpressed in 85-90% of oncogenic cells but not normal body cells. There are an abundance of reports recitation their antitumor, anticancer and antioxidant properties. Prime responsibility of flavonoids, as effective G-4 binding agents. Earlier it has been mentioned through different optical spectral techniques that Quercetin, a naturally taking place in flavonoids, interact with single and double polymeric forms of G-4 motif from end to end amassing and hollow binding mode correspondingly [7]. Another oncogene supporter gene contains the 23-nt bcl-2 promotor sequence 5'-G3CGCG3AG2A2T2G3 CG3-3' also formed the intramolecular G-quadruplex, its quite analogous to the [3+1] G-4 scaffold [8,9]. It has likewise the capability to temper the gene copy process. HIV-1 integrase in which the produce small molecular ligand. These are confirmed by means of the CD, NMR, and molecular docking techniques. The interface monomer especially two must be an anti-anti-anti-syn alignment that held guanine both sides from another monomer [3+1type] [10,11]. The various different locked interface interlocked dimeric forms of G-quadruplex are more stable, this is the reason that acts as the biological application, it serves as molecular target canyon of the multimeric protein. The various different locked interface interlocked dimeric forms of G-quadruplex are more stable, this is the reason that acts as the biological application, it serves as molecular target canyon of the multimeric protein [12]. Double stuck G-quadruplex. Usually, supplementary about one form of G-4 hardly ever reported double-stranded G quadruplex twisted by the repeating unit of guanine territory. The oblique loop of the G-quadruplex can be fashioned in the Oxycyrica nova telomeric d(G4T4G4) [13] arrangement these in sequence about key assembly and crystal assembly acquired by the x-ray crystallography and NMR spectroscopy [14].

The two T4 sequences that formed the in this G-quadruplexes these loops operation as a connector as anti- anti-syn-syn G scaffold these obliquely cross it maximum and bottommost faced about the G-quadruplex. In the twofold stuck G-quadruplex has one extensive one slender and two intermediate hollows [15].

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Indazole Heterocyclic Molecules for stabilization of Groove

Indazole nucleus is most profound, contains numerous biological activity, it's nitrogen-containing heterocyclic moiety [23]. It formed by the fusion of two rings one is benzene and pyrazole. Indazole nucleus having the ability to convert in their tautomerized form; its mentioned below 1*H*-indazole, 2*H*- indazole and last is 3*H*-indazole [24]. The stability is the more prominent towards the 1*H*-indazole rest of the two are not as stable as the first one. Recently, being a heterocyclic nucleus it pays considerable focus to deal with these scaffolds. Indazole derivatives do not occur in nature, having a wide range pharmacological activities such as anti-tumor, anti-inflammatory, anti-fungal, etc. Indazoles nucleus is a planar heterocyclic ring, so its substituted derivatives have numerous bioactivity. In several drug molecules such as niraparib have indazole core exhibit potential towards the treatment of cancer (epithelial ovarian, fallopian tube and breast cancer also in protest of cancer).

Synthesis scheme of 1*H*- indazole

A reported method that used in synthesis of indazole from aminohydrazone by intra-molecular ligandfree catalyzed by palladium C-H amination reaction [25].

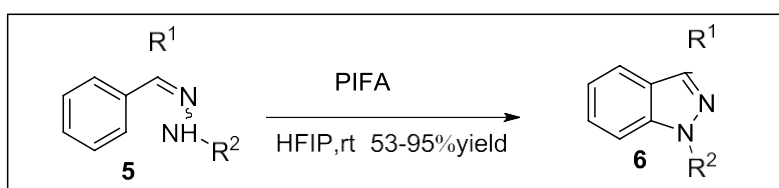


Figure 5: synthetic scheme of indazole.

Synthetic scheme of 2*H*-indazole

The synthesis of another tautomer 2*H*- indazole reveal by Nazare at al.[26] an organophosphorus mediated reductive cyclization further coming N,N dimethyl substituted benzamidines that lead to the formation of 3-amino-2*H*-indazole and this moiety derived from the 2-nitrobenzonitril.

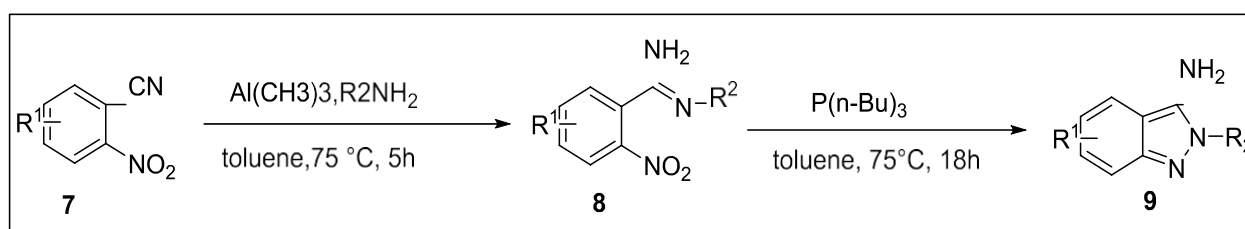


Figure 6 : synthetic scheme of 2*H*- indazole

In corresponding to reaction synthesis of the N-aryl-2*H*-indazoles by $Cp^*Co(iii)$ leads to C-H bond functionalization, treated the azobenzene with aldehyde [27] within presence reagents in reaction [28]. The researcher further realized that cyclization of azobenzene with α - ketoaldehydes is also possible by this method synthesis of 3-acetylated 2*H*- indazole more efficiently done [30].

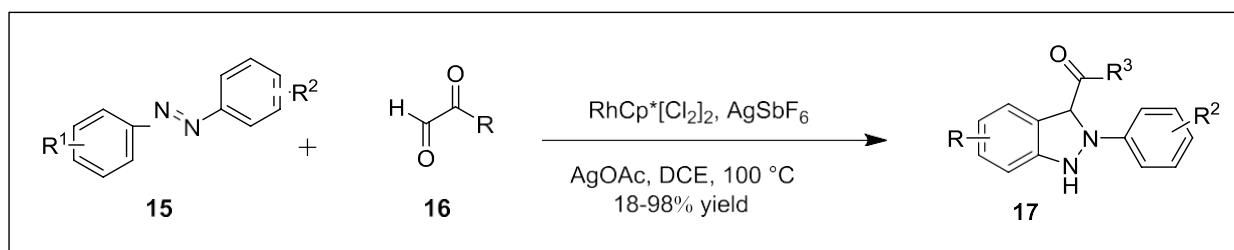


Figure 7: synthetic scheme of 2H-indazole by rhodium catalyzed from azobenzene and α keto.

Potential Role for Regulation of Different tumor:

Blockade of EGFR

The epidermal growth factor receptor involved the prime family of Tyrosine kinase receptor or erbB family. This large receptor family contain four different subfamily EGFR (ErbB1/HER1), (erbB2/HER3), (erbB3/HER3) and (erbB4/HER4) [31]. These all tyrosine kinase receptors play a crucial role in down-regulation, it consists of multilayer networks that permit the horizontal interaction and show the multiple responses. Disturbance in their normal signaling networks provokes several types of malignancy such as breast, prostate, ovarian and stomach cancer.

The cell membrane has an extracellular-ligand binding domain that is a trans-membrane segment consist of intracellular tyrosine kinase contain carboxyl terminal [32].

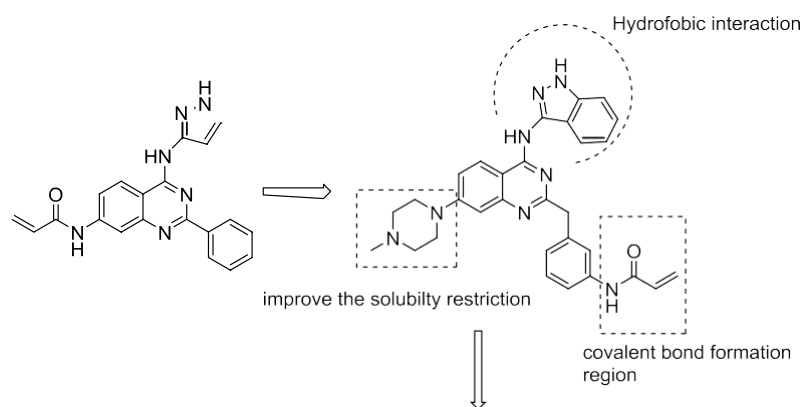


Figure: 8 EGRF inhibitors.

The inhibition of these deregulated signaling pathways small molecules are quite effective forms inactive homodimer of receptor through the compete with ATP binding site, EGFR (erbB/HER) forms dimer complex.

Inhibition of FGFRs

The fibroblast growth factor receptor is incorporate in several physiological functions such as growth, proliferation and the importantly plays a key role in neoplastic behavior [33]. The FGF/FGFRs trans- membrane receptor exposed to single point mutation, especially (FGFR3) create orthopedic disorders further initiates dwarfism, and craniofacial disorder. Some of these expressed in human also that leads to several types of cancer [34]. In the human bio-signaling (especially FGF/FGFRs) abrupton provoke the change in their functional behavior, causing malignancies such as breast squamous lung carcinomas (Head and neck). The molecular-based targeted therapy that involved the better downfall in NSCLC due to the effective EGFR-TKIs, gets mutated or not respond well by alteration in gatekeeper or enlargement of the EGFR. Other consequences are it bypass the mutation in HGF-MET and PI3KCA mutation through

changing their normal signaling pathways.

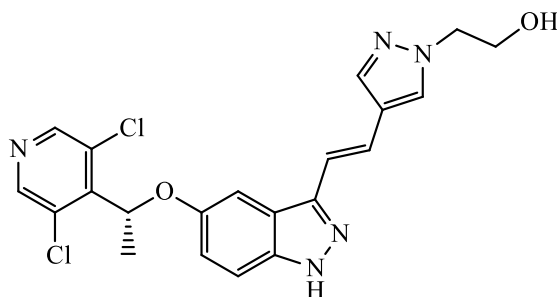


Figure: 9 Design of FGFR blocker.

The reported data suggested that the available selective inhibitors like AZD4547, NVP-BGJ 398 and PD173074 blocks the ATP binding site due to 3,5-dimethoxydiphenyl moiety[35].

Blockade of VEGFRs

Angiogenesis term describes the extensive spread network of the blood vessels that helps out to nurtures, the tissues by supplying that proper oxygen and nutrition. The endothelial cell line provides supportive growth for inner development for the blood vessels [36]. Their abnormal function provoking many consequences like ischemia and inflammatory disease, the continuous abnormal growth of blood vessels leading the hallmark of cancer. The VEGFRs and notch co-operating acts as branching and differentiating by integrated feedback. VEGF stimulates the cell tip induction via VEGFR2 and VEGFR3 expressed in the embryonic vasculature but it convert moderate to lymphocyte [37].

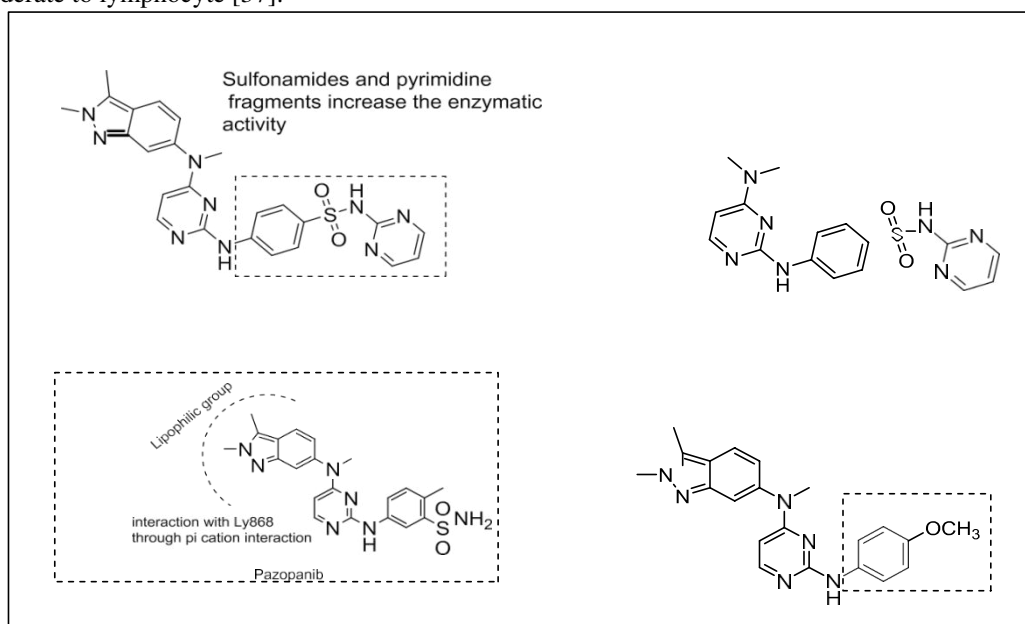


Figure : 10 Indazole derivatives as VEGFRs blocker.

In the pazopanib the activity against VEGFR2 displayed by the substituted sulfonamide and pyrimidine fragments, its activity also noticed against the platelets derived growth factor (PDGFR- α and β) c-kit stem cell receptor [38]. The anti-angiogenic drugs are not feasible for the children or pregnant lady in case of inflammatory disorder like arthritis, however, it is used only in case of nonsolid tumor.

II. CONCLUSION

The G-quadruplex design is a significant optional design of nucleic acids. The broad presence in essential administrative genome districts and a progression of revealed natural capabilities make this design a promising medication focus in enemy of cancer drug disclosure. In this survey, we examine the designs, presence, and elements of G-quadruplexes. Basing on this, we sum up some normal G-quadruplex ligands with promising enemy of cancer exercises. Since G-quadruplexes apply their administrative capabilities essentially through the limiting proteins of various nucleic acids, particularly the helicases, we further present some G-quadruplex-related proteins, particularly the helicase. The way that planning atoms to hinder the connections between nucleic acids and proteins is possible makes this original enemy of cancer procedure increasingly alluring.

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